

# Example of a biochemical cascade: Mitogen Activated Protein Kinase (MAPK) in Solution

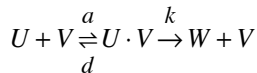
## MAPK CASCADE

MAPK gives a canonical example of a phosphorylation cascade, a sequence of phosphorylation reactions where the active, or phosphorylated form (sometimes doubly-phosphorylated form), of a protein at the  $k$ th step of the cascade subsequently catalyzes phosphorylation of the protein on the  $k+1$ st step of the cascade.

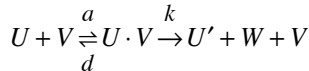
## NOTATION USED FOR REACTIONS

We might represent a catalytic (e.g., enzymatic) reaction in (at least) the following four different ways:

1.  $V \Rightarrow W$ , read as “V activates W,” e.g., V catalyzes the formation of an object called W (V may be an enzyme and W its product). It is not clear in this notation what W is formed from (the source) or what rate constants (and other data) describe this process.
2.  $U \xRightarrow{V} W$ , read as “V facilitates the conversion of U to W,” e.g., when V is an enzyme with substrate U and product W. Rate constants and other potential reactants (such as Ca or ATP) are still hidden, and it is not clear whether U is converted into W or if U still remains, perhaps in an altered form, after the reaction occurs.
3. As a biochemical reaction such as

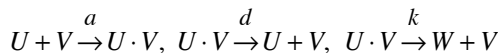


where  $U \cdot V$  is the molecular complex formed by combining U and V, and  $a$ ,  $d$  and  $k$  are rate constants. In this reaction U is converted into (and is assumed to replace) W. Other reactants are still suppressed. In an alternative scheme, U is replaced by two products,  $U'$  and W,

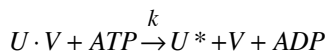


We will focus on the first scheme only.

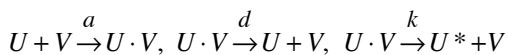
4. As a set of basic chemical reactions such as



Here U is literally converted into W by V. In the case of phosphorylation we might actually want to replace the third reaction with



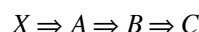
where  $U^*$  the phosphorylated version of U. In general we will assume that there is ample ATP available for phosphorylation to occur, and we will instead write the set of reactions as



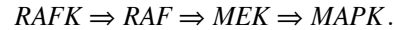
with similar notation for the removal of phosphate groups. The following examples apply specifically to a **phosphorylation** cascade.

## SIMPLE CASCADE NOTATION:

A cascade would be written as

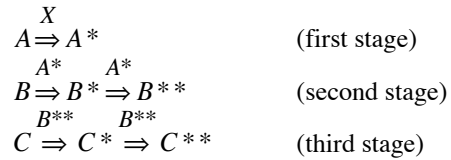


which we would read as “X activates A, A activates B, B activates C.” An example would be



## MORE DETAILED CASCADE NOTATION

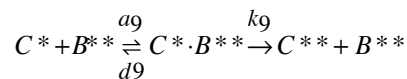
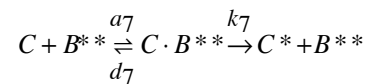
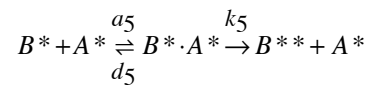
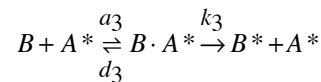
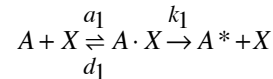
In this notation we explicitly show the “input,” “output,” and “catalyst” of each state. A three-stage MAP kinase cascade would be written as



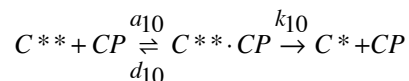
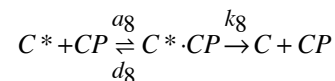
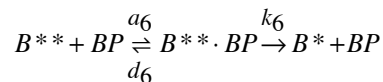
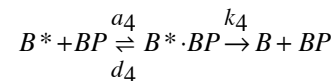
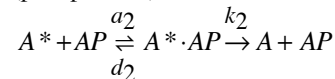
We read this as: “X phosphorylates A, the phosphorylated form A (called  $A^*$ ) phosphorylates B twice, and the doubly phosphorylated form of B phosphorylates C twice.” The input to the cascade is X and the output is  $C^{**}$ . More common names for A, B and C are MAPKKK, MAPKK, and MAPK, respectively. A typical example would be RAF (MAPKKK), MEK (MAPKK) and MAPK, with the input signal being RAFK (RAF kinase).

## BIOCHEMICAL REACTIONS

### Actual Phosphorylation Reactions:



### Reverse Enzyme (phosphatase) Reactions:



## DIFFERENTIAL EQUATIONS:

### Protein concentrations: Input Signal Protein

$$[X]' = -a_1[A][X] + (d_1 + k_1)[A \cdot X]$$

### Protein concentrations: First Stage of Cascade

$$[A]' = -a_1[A][X] + d_1[A \cdot X] + k_2[A^* \cdot AP]$$

$$[A^*]' = -a_2[AP][A^*] - a_3[A^*][B] - a_5[A^*][B^*] + d_2[A^* \cdot AP] \\ + (d_3 + k_3)[B \cdot A^*] + (d_5 + k_5)[B^* \cdot A^*] + k_1[A \cdot X]$$

### Protein concentrations: Second Stage of Cascade

$$[B]' = -a_3[A^*][B] + d_3[B \cdot A^*] + k_4[B^* \cdot BP]$$

$$[B^*]' = -a_4[BP][B^*] - (a_5 - d_5)[A^*][B^*] \\ + d_4[B^* \cdot BP] + k_3[B \cdot A^*] + k_6[B^{**} \cdot BP]$$

$$[B^{**}]' = -a_6[BP][B^{**}] - a_7[B^{**}][C] - a_9[B^{**}][C^*] \\ + d_6[B^{**} \cdot BP] + (d_7 + k_7)[C \cdot B^{**}] \\ + (d_9 + k_9)[C^* \cdot B^{**}] + k_5[B^* \cdot A^*]$$

### Protein concentrations: Third Stage of Cascade

$$[C]' = -a_7[B^{**}][C] + d_7[C \cdot B^{**}] + k_8[C^* \cdot CP]$$

$$[C^*]' = -a_8[CP][C^*] - a_9[B^{**}][C^*] + d_8[C^* \cdot CP] \\ + d_9[C^* \cdot B^{**}] + k_{10}[C^{**} \cdot CP] + k_7[C \cdot B^{**}]$$

$$[C^{**}]' = -a_{10}[CP][C^{**}] + d_{10}[C^{**} \cdot CP] + k_9[C^* \cdot B^{**}]$$

### Intermediate Complex Concentrations:

$$[A \cdot X]' = a_1[A][X] - (d_1 + k_1)[A \cdot X]$$

$$[B^* \cdot A^*]' = a_5[A^*][B^*] - (d_5 + k_5)[B^* \cdot A^*]$$

$$[B \cdot A^*]' = a_5[A^*][B] - (d_3 + k_3)[B \cdot A^*]$$

$$[C^* \cdot B^{**}]' = a_9[B^{**}][C^*] - (d_9 + k_9)[C^* \cdot B^{**}]$$

$$[C \cdot B^{**}]' = a_7[B^{**}][C] - (d_7 + k_7)[C \cdot B^{**}]$$

### Phosphatase Concentrations:

$$[AP]' = -a_2[AP][A^*] + (d_2 + k_2)[A^* \cdot AP]$$

$$[BP]' = -a_4[BP][B^*] - a_6[BP][B^{**}] + \\ (d_4 + k_4)[B^* \cdot BP] + (d_6 + k_6)[B^{**} \cdot BP]$$

$$[CP]' = -a_{10}[CP][C^{**}] - a_8[CP][C^*] \\ + (d_8 + k_8)[C^* \cdot CP] + (d_{10} + k_{10})[C^{**} \cdot CP]$$

### Intermediate Concentrations (with Phosphatase in complex)

$$[A^* \cdot AP]' = a_2[AP][A^*] - (d_2 + k_2)[A^* \cdot AP]$$

$$[B^* \cdot BP]' = a_4[BP][B^*] - (d_4 + k_4)[B^* \cdot BP]$$

$$[B^{**} \cdot BP]' = a_6[BP][B^{**}] - (d_6 + k_6)[B^{**} \cdot BP]$$

$$[C^* \cdot CP]' = a_8[CP][C^*] - (d_8 + k_8)[C^* \cdot CP]$$

$$[C^{**} \cdot CP]' = a_{10}[CP][C^{**}] - (d_{10} + k_{10})[C^{**} \cdot CP]$$